REMARKS

Applicant respectfully requests reconsideration. Claims 1-9, 12, and 25 were previously pending in this application. Claims 1-6 have been amended. Support for the claim amendments may be found in the specification (for example, page 3, line 1 – page 4, line 31; and the Figures). Claims 26-32 have been added. Claims 12 and 25 have been cancelled. Claims 1-9 and 26-32 remain pending with claims 1, 28 and 31 being independent. No new matter has been added.

In all instances herein where reference to the specification of the instant application is made, references is made to the corresponding published PCT application (International Patent Publication WO 04/026850); copy enclosed.

Objections to the Claims

Claim 12 was objected to as being of improper dependent form for failing to further limit the subject matter of the previous claim. Without acceding to the merits of the rejection, Applicant has cancelled claim 12.

Therefore, withdrawal of the objection based on this ground is respectfully requested.

Rejection of Claims 2, 3, and 12 under 35 U.S.C. §112, second paragraph

Claims 2, 3, and 12 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Without acceding to the merits of the rejection, Applicant has amended claims 2-3 and has cancelled claim 12.

Therefore, withdrawal of the objection based on this ground is respectfully requested.

Rejection of Claims 1-9, 12, and 25 under 35 U.S.C. §112, first paragraph

Claims 1-9, 12, and 25 were rejected under 35 U.S.C. §112, first paragraph, because, according to the Patent Office, the specification does not enable any person skilled in the art to which it pertains, or with which it is most closely connected, to make the invention commensurate in scope with these claims. Applicant respectfully disagrees.

Applicant notes that the Patent Office must consider not just a single factor, but a totality of the circumstances involving many factors when making a determination that the application is not enabled. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicant submits that an analysis of the *Wands* factors weighs in favor of Applicant's assertion of enablement over the full scope of the claims, as discussed in detail below.

Breadth of the Claims

The breadth of the claims is reasonable in view of the teaching in the specification, as described further below in view of the other *Wands* factors. It is noted that the claims are not so broad as to encompass processes for preparing 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles including any functional group(s). Instead, the claims include significant structural limitation. The claimed system must be a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole having a structure as indicated in structure 5a and substituted with one or more of the groups listed in claim 1. While claim 1 covers a process for preparing a variety of compounds and is not limited to the preparation of one, specific compound, those of ordinary skill in the art would easily be able to select, without undue experimentation, suitable starting materials for use in the context of the invention to prepare a particular desired compound.

The Nature of the Invention

The nature of the invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles that may be substituted with a variety of functional groups. As noted above, those of ordinary skill in the art would be able to select suitable starting materials for use in the invention, to prepare a particular desired compound without undue experimentation.

The State of the Prior Art

The state of the prior art is advanced. Various starting materials which are capable of being used in the context of the present invention to obtain a particular, desired product, are well-known to those of ordinary skill in the art, as described in the specification and in references of record in this application (please see page 11, lines 12-18 of the specification). Further, the design and synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles using a wide variety of starting material is aided by knowledge in the art related to the compatibility of various functional groups with processes as described in the present invention. For example, with the benefit of the present

specification, those of ordinary skill in the art would expect the functional groups listed in claim 1 to generally be compatible with (e.g., inert to) the reaction conditions utilized in the process of claim 1.

The Level of Ordinary Skill in the Art

The level of ordinary skill in the art is high. The relevant art is synthetic organic chemistry, and the skilled artisan is generally familiar with methods for synthesizing a wide variety of compounds, such as 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles by, with the benefit of the present specification, varying the starting materials used in a synthetic process, such as a process of claim 1.

The Level of Predictability of the Art

With respect to starting materials which are suitable for use in the process described in claim 1, and with the benefit of the present specification, the predictability of the art is reasonably high. Those of ordinary skill in the art would be able to select, using the teachings of the specification, appropriate starting materials for use in the present invention to obtain a particular, desired product with a high level of predictability. For example, those of ordinary skill in the art would be able to select a protected cyclohexanedione starting material, an amine starting material, or a thiourea starting material, each having one or more functional groups, to produce a desired 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole as described in the present invention, wherein the functional group(s) are substantially inert to reaction conditions used in processes of the invention.

The Amount of Direction Provided

The amount of direction provided by the Applicant in the specification is substantial. Applicant provides, in the working examples and in the specification, techniques that are applicable to various starting materials in the synthesis of substituted 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles. Those of ordinary skill in the art would be able to readily select and/or prepare starting materials, including numerous commercially available starting materials, that may be used in the claimed process, using the teachings of the specification. For example, the specification includes examples of a wide range of starting materials and reagents suitable for use in the present invention (page 5, line 18 – page 7, line 10; and the Figures).

The Existence of Working Examples

Applicant has provided three working examples demonstrating synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles using the teachings in the specification. The methods described in the examples are not only applicable to the specific compounds described, but many of these methods may be applied to synthesize a variety of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles without any level of undue experimentation. For example, the examples teach the synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles containing alkyl groups, which those of ordinary skill in the art would be able to modify using routine experimentation by the use of different starting materials, i.e., other substituted protected cyclohexanediones, substituted amines, and substituted thioureas.

The Quantity of Experimentation Needed

The amount of experimentation required to practice within the scope of the claims that stand rejected on this ground, in view of the totality of teachings of the specification of this application and the state of the art, is routine experimentation. Starting materials which may be used to form 4,5,6,7-tetrahydro-6-aminobenzothiazoles, in general, are readily available, and one of ordinary skill in the art can determine which starting materials, or combination of starting materials, would be suitable for use in the present invention without undue experimentation. Screening for such compounds, if not quickly identified in other ways, would be routine. A survey of the prior art (references included in the specification and of record in the present application) provides evidence of the fact that such starting materials in general are known to those skilled in the art.

Therefore, a full and fair analysis of the *Wands* factors strongly suggests that the Applicant has enabled the claimed invention throughout its full scope.

Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection of Claims 1-9, 12, and 25 under 35 U.S.C. §103(a)

Claims 1-9, 12, and 25 were rejected under 35 U.S.C. §103(a) as being unpatentable over European Patent No. EP 0207696A1 ("Leguzza") in view of Solomons et al., Organic Chemistry 2008, 9th Edition, John Wiley & Sons, Inc., page 224-236 ("Solomons"). Specifically, the Office Action states that, because Solomons teaches that iodine is a better leaving group than bromine, it

would have been obvious to one of ordinary skill in the art at the time that the invention was made to substitute iodine for bromine in the process of Leguzza, to obtain the process recited in claim 1. Applicant respectfully traverses the rejection.

As an initial matter, Applicant disagrees with the assertion by the Patent Office that the alpha-bromoketone formed in Leguzza is not isolated. Leguzza clearly states that bromine and hydrobromide are "removed *in vacuo* to leave a brown viscous oil comprising 2-bromo-4-di-n-propylaminocyclohexanone," (page 13, lines 20-23, of Leguzza) indicating that the alpha-bromoketone formed in Leguzza, while not fully purified or characterized, is isolated.

Applicant sees no motivation or suggestion in Leguzza or Solomons to combine the teachings of Leguzza and Solomons in the manner stated in the Office Action. By contrast, those of ordinary skill in the art would expect that the use of iodine in the Leguzza process would produce an alpha-iodoketone that is highly unstable, relative to the corresponding alpha-bromoketone. Those of ordinary skill in the art would also expect that the alpha-haloketone intermediate could not be isolated. Thus, there would be no reasonable expectation of success in modifying the process of Leguzza with the teaching of Solomons.

Furthermore, Applicant notes that, in determining the differences between the prior art and the claimed invention, Patent Office has not considered whether the claimed invention as a whole would have been obvious. In addition to the use of bromine and hydrobromide to form an alpha-bromoketone, Leguzza differs from the present invention in that the process disclosed in Leguzza involves the separate steps of (1) forming an isolated alpha-bromoketone and (2) subsequently adding thiourea to the isolated alpha-bromoketone, to form the product. Applicant also notes that, in the Leguzza process, the alpha-bromoketone is formed in the presence of volatile reagents including bromine, hydrobromic acid, and acetic acid. By contrast, the process recited in claim 1 does not require the isolation of the alpha-haloketone intermediate and does not employ the use of bromine, hydrobromic acid, and acetic acid.

As such, Applicant sees no motivation or suggestion in Leguzza or Solomons to make any modification to Leguzza process that would result in the invention as recited in claim 1. Therefore, claim 1 is not unpatentable over Leguzza in view of Solomons for at least this reason. Claims 2-9 depend from claim 1 and, therefore, are also not unpatentable over Leguzza in view of Solomons.

Accordingly, withdrawal of the rejection of these claims is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

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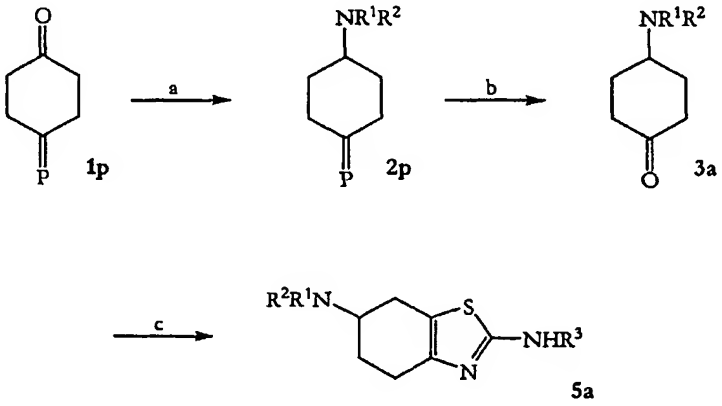
(54) Title: PROCESS FOR THE PREPARATION OF 2-AMINO-4,5,6,7-TETRAHYDRO-6-AMINOBENZOTHIAOLES FROM CYCLOHEXANES AND CYCLOHEXANONES AS INTERMEDIATES



a: reductive amination with R^1R^2NH
b: deprotection
c: (i) iodine, $H_2N(C=S)NHR^3$; (ii) OH^-

(57) Abstract: The present invention relates to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles (5a) from cyclohexanes (2a) and cyclohexanones (3a) as intermediate.

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— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

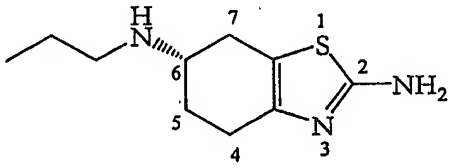
PROCESS FOR THE PREPARATION OF 2-AMINO-4,5,6,7-TETRAHYDRO-6-AMINOBENZOTHIAZOLES FROM CYCLOHEXANES AND CYCLOHEXANONES AS INTERMEDIATES

Technical field

The present invention relates to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles and to novel cyclohexanes and cyclohexanones for use in these processes.

Background art

Certain 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are known to have dopamine D-2 activity and are therefore potentially useful as pharmaceuticals for the treatment of psychiatric disorders such as schizophrenia and Alzheimer's disease. One such compound, the dihydrochloride salt of (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole I (pramipexole), is marketed as a pharmaceutical for the treatment of Parkinson's disease. The numbering of pramipexole I is indicated below.



I

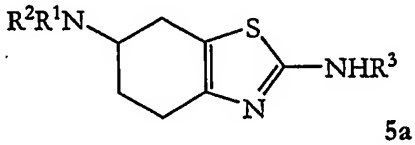
Processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are disclosed in patents US 4843086, US 4886812 and patent applications WO 02/22590 A1 and WO 02/22591 A1. A procedure to these types of compound is also disclosed by C.S. Schneider and J. Mierau in J. Med. Chem., 1987, vol. 30, pages 494-498.

However, known processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are not satisfactory, particularly for industrial scale manufacture, as they have been found to be low yielding and involve the use of

hazardous and difficult to handle reagents such as bromine, hydrazine and potassium chromate.

Summary of the invention

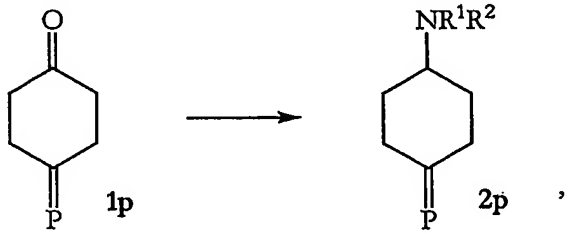
A first aspect of the present invention is a process for the preparation of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a



5a

or a salt thereof, comprising the steps of:

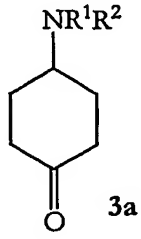
(a) reductively aminating a protected cyclohexandione **1p** with an amine R^1R^2NH to yield a protected 4-amino-cyclohexanone **2p**:



1p **2p** ,

wherein P is a protected ketone functionality, and R^1 and R^2 are any atom or group or, together with the nitrogen to which they are attached, form a ring;

(b) deprotecting the protected 4-amino-cyclohexanone **2p** to yield an unprotected 4-amino-cyclohexanone **3a**



3a ; and

(c) treating the unprotected 4-amino-cyclohexanone **3a** with iodine and a substituted thiourea $H_2N(C=S)NHR^3$, wherein R^3 is any atom or group, to yield the 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof.

For the purposes of the present invention, an "alkyl" group is defined as a monovalent saturated hydrocarbon, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkyl groups are methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl and *n*-pentyl groups. Preferably an alkyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkyl group is a C_1-C_{12} alkyl group, which is defined as an alkyl group containing from 1 to 12 carbon atoms. More preferably an alkyl group is a C_1-C_6 alkyl group, which is defined as an alkyl group containing from 1 to 6 carbon atoms. An "alkylene" group is similarly defined as a divalent alkyl group.

An "alkenyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon double bond, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkenyl groups are vinyl, allyl, but-1-enyl and but-2-enyl groups. Preferably an alkenyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkenyl group is a C_2-C_{12} alkenyl group, which is defined as an alkenyl group containing from 2 to 12 carbon atoms. More preferably an alkenyl group is a C_2-C_6 alkenyl group, which is defined as an alkenyl group containing from 2 to 6 carbon atoms. An "alkenylene" group is similarly defined as a divalent alkenyl group.

An "alkynyl" group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon triple bond, which may be straight-chained or branched, or be or include cyclic groups. Examples of alkynyl groups are ethynyl, propargyl, but-1-ynyl and but-2-ynyl groups. Preferably an alkynyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkynyl group is a C_2-C_{12} alkynyl group, which is defined as an alkynyl group containing from 2 to 12 carbon atoms. More preferably an alkynyl group is a C_2-C_6 alkynyl group, which is defined as an alkynyl group containing from 2 to 6 carbon atoms. An "alkynylene" group is similarly defined as a divalent alkynyl group.

An "aryl" group is defined as a monovalent aromatic hydrocarbon. Examples of aryl groups are phenyl, naphthyl, anthracenyl and phenanthrenyl groups. Preferably

an aryl group does not include any heteroatoms in its carbon skeleton. Preferably an aryl group is a C_4-C_{14} aryl group, which is defined as an aryl group containing from 4 to 14 carbon atoms. More preferably an aryl group is a C_6-C_{10} aryl group, which is defined as an aryl group containing from 6 to 10 carbon atoms. An "arylene" group is similarly defined as a divalent aryl group.

Where a combination of groups is referred to as one moiety, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule. A typical example of an arylalkyl group is benzyl.

For the purposes of this invention, an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group may be substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$, -COOH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-R^4-SO-R^5$, $-R^4-SO_2-R^5$, $-R^4-SO_2-OR^5$, $-R^4O-SO_2-R^5$, $-R^4-SO_2-N(R^5)_2$, $-R^4-NR^5-SO_2-R^5$, $-R^4O-SO_2-OR^5$, $-R^4O-SO_2-N(R^5)_2$, $-R^4-NR^5-SO_2-OR^5$, $-R^4-NR^5-SO_2-N(R^5)_2$, $-R^4-N(R^5)_2$, $-R^4-N(R^5)_3^+$, $-R^4-P(R^5)_2$, $-R^4-Si(R^5)_3$, $-R^4-CO-R^5$, $-R^4-CO-OR^5$, $-R^4O-CO-R^5$, $-R^4-CO-N(R^5)_2$, $-R^4-NR^5-CO-R^5$, $-R^4O-CO-OR^5$, $-R^4O-CO-N(R^5)_2$, $-R^4-NR^5-CO-OR^5$, $-R^4-NR^5-CO-N(R^5)_2$, $-R^4-CS-R^5$, $-R^4-CS-OR^5$, $-R^4O-CS-R^5$, $-R^4-CS-N(R^5)_2$, $-R^4-NR^5-CS-R^5$, $-R^4O-CS-OR^5$, $-R^4O-CS-N(R^5)_2$, $-R^4-NR^5-CS-OR^5$, $-R^4-NR^5-CS-N(R^5)_2$ or $-R^5$. In this context, $-R^4-$ is independently a chemical bond, a C_1-C_{10} alkylene, C_1-C_{10} alkenylene or C_1-C_{10} alkynylene group. $-R^5$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_6-C_{10} aryl. Optional substituent(s) are not taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituent(s).

Any optional substituent may be protected. Suitable protecting groups for protecting optional substituents are known in the art, for example from "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991).

For the purposes of this invention, a "salt" is any acid addition salt, preferably a pharmaceutically acceptable acid addition salt, including but not limited to a hydrohalogenic acid salt such as hydrofluoric, hydrochloric, hydrobromic and hydroiodic acid salt; an inorganic acid salt such as nitric, perchloric, sulfuric and phosphoric acid salt; an organic acid salt such as a sulfonic acid salt (for example methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, isethionic, benzenesulfonic, p-toluenesulfonic or camphorsulfonic acid salt), acetic, malic, fumaric, succinic, citric, tartaric, benzoic, gluconic, lactic, mandelic, mucic, pamoic, pantothenic, oxalic and maleic acid salt; and an aminoacid salt such as ornithinic, glutamic and aspartic acid salt. The acid addition salt may be a mono- or di-acid addition salt. A preferred salt is a di-hydrohalogenic, di-sulphuric, di-phosphoric or di-organic acid salt. A most preferred salt is a di-hydrochloric acid salt.

P is a protected ketone functionality. Suitable protecting groups are commonly known in the art, for example from Chapter 4 of "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991).

Preferably the protected ketone functionality P is an acyclic ketal or derivative **1q**, a cyclic ketal or derivative **1r**, **1s** or **1t**, or a hydrazone or oxime **1u**, as shown in Figure 4. More preferably P is a cyclic ketal **1r**, most preferably P is a monoethyleneketal **1**, as shown in Figures 2 and 3.

R^1, R^2 and R^3 can be any atom or group. Preferably R^1 and R^2 are not amine protecting groups. Amine protecting groups are commonly known in the art, for example from Chapter 7 of "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 2nd edition, 1991). Most preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton. Such an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton, does not encompass carbonyl -CO-R groups, wherein R is any atom or group.

Optionally R^1, R^2 and R^3 are independently hydrogen or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton.

Optionally R^1, R^2 and R^3 are independently an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton, and which may be optionally substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$, -COOH, $-R^4-O-R^5$, $-R^4-S-R^5$, $-R^4-SO-R^5$, $-R^4-SO_2-R^5$, $-R^4-N(R^5)_2$, $-R^4-Si(R^5)_3$, $-R^4-CO-R^5$, $-R^4-CO-OR^5$, $-R^4O-CO-R^5$, $-R^4-CO-N(R^5)_2$, $-R^4-NR^5-CO-R^5$, $-R^4-CS-R^5$ or $-R^5$, wherein

$-R^4-$ is independently a chemical bond, a C_1-C_{10} alkylene, C_1-C_{10} alkenylene or C_1-C_{10} alkynylene group, and

$-R^5$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_6-C_{10} aryl.

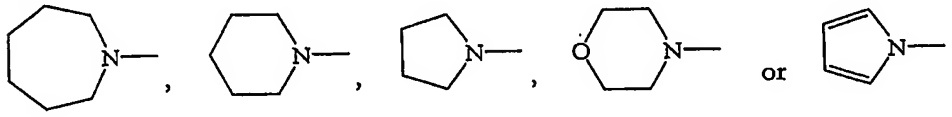
Optionally R^1, R^2 and R^3 are independently an alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which does not include any heteroatoms in its carbon skeleton, and which may be optionally substituted with one or more of -F, -Cl, -Br, -I, $-CF_3$, $-CCl_3$, $-CBr_3$, $-CI_3$, -OH, -SH, $-NH_2$, -CN, $-NO_2$, -COOH, $-OR^5$, $-SR^5$, $-SO-R^5$, $-SO_2-R^5$, $-N(R^5)_2$, $-Si(R^5)_3$, $-CO-R^5$, $-CO-OR^5$, $-O-CO-R^5$, $-CO-N(R^5)_2$, $-NR^5-CO-R^5$, $-CS-R^5$ or $-R^5$, wherein

$-R^5$ is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_6-C_{10} aryl.

Preferably R^1, R^2 and R^3 are independently hydrogen or an unsubstituted alkyl, aryl or heteroaryl group, which does not include any heteroatoms N, O or S in its carbon skeleton. More preferably, R^1, R^2 and R^3 are independently hydrogen or an unsubstituted C_{1-10} alkyl group. More preferably, R^1, R^2 and R^3 are independently hydrogen or an unsubstituted C_{1-6} alkyl group. More preferably, one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an unsubstituted C_{1-6} alkyl group, and R^3 is

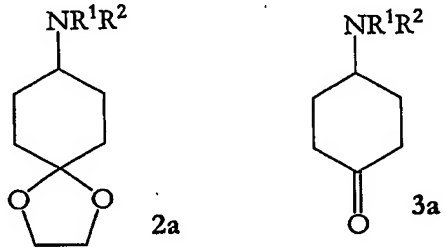
hydrogen. Most preferably, one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl, and R^3 is hydrogen.

Alternatively, R^1 and R^2 can, together with the nitrogen to which they are attached, form a ring. Optionally $-NR^1R^2$ together form an optionally substituted heterocycloalkyl, heterocycloalkenyl or heteroaryl ring. Optionally $-NR^1R^2$ together form



Preferably the reductive amination of step (a) is carried out with $NaCNBH_3$.

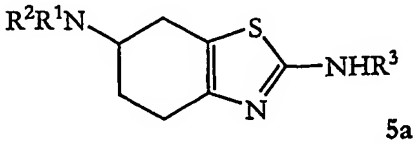
A second aspect of the present invention is a 4-amino-cyclohexanone-ethyleneketal **2a** or a 4-amino-cyclohexanone **3a**



2a **3a**

for use in a process of the first aspect of the present invention. R^1 and R^2 are as defined above with reference to the first aspect of the present invention. Preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl.

A third aspect of the present invention is a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a**



5a

or a salt thereof, obtained by a process of the first aspect of the present invention. R^1, R^2 and R^3 are as defined above with reference to the first aspect of the present

invention. Preferably one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl, and R^3 is hydrogen. Preferably the compound is a di-hydrochloric acid salt.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** or salts thereof have at least one chiral centre and can therefore exist in the form of various stereoisomers. The present invention embraces all of these stereoisomers and mixtures thereof. Mixtures of these stereoisomers can be resolved by conventional methods, for example, chiral chromatography, fractional recrystallisation, derivatisation to form diastereomers and subsequent resolution, and resolution using enzymes.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or salt thereof of the present invention preferably comprises at least 95% of the (R)- or the (S)-enantiomer, preferably at least 98% of the (R)- or the (S)-enantiomer, and more preferably at least 99% of the (R)- or the (S)-enantiomer. Generally, the (S)-enantiomer is the preferred enantiomer.

The 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or salt thereof may be used as a medicament, preferably for the treatment of a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease.

A fourth aspect of the present invention is a pharmaceutical composition, comprising 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or salt thereof and a pharmaceutically acceptable carrier or diluent. Preferably the pharmaceutical composition is suitable for the treatment of a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease.

A fifth aspect of the present invention is a method of treating a psychiatric or neurological disorder such as schizophrenia, Alzheimer's disease or Parkinson's disease, comprising administering a therapeutically effective amount of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof to a subject in need of such treatment.

Brief description of the drawings

Figure 1 is a schematic illustration of the process of the present invention.

Figures 2 and 3 are schematic illustrations of preferred processes of the present invention.

Figure 4 illustrates preferred protected ketone functionalities P.

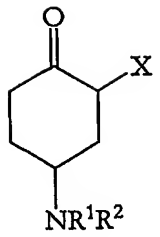
Detailed description of the invention

The inventors have found that processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** are greatly improved by the process outlined in Figure 1, wherein R^1 and R^2 can be any atom or group or, together with the nitrogen to which they are attached, form a ring, and wherein R^3 can be any atom or group. R^1, R^2 and R^3 are preferably hydrogen or an unsubstituted alkyl, aryl or heteroaryl group.

The process outlined in Figure 1 is short, utilises a readily available starting material, a protected cyclohexandione **1p**, and does not require any hazardous chemical reagents. Each step of the process is high yielding and affords products of very high purity.

Therefore a first aspect of the current invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** by the process specified in Figure 1.

It has been disclosed in prior art documents WO 02/22590 and WO 02/22591 that, in practice, compounds of formula **5a**, comprising a primary amino or a secondary alkylamino group, cannot be prepared directly from the corresponding ketones **3a**. The process shown in Figure 1, however, illustrates that the process of the current invention does indeed allow a compound **5a** to be prepared from ketones **3a** directly without the requirement of preparing and isolating an α-haloketone of formula 4, where X is a halide such as chloride or bromide, or the requirement of a protecting group on the nitrogen atom of the amine substituent $-NR^1R^2$ of the ketone **3a**.



4

Therefore, in a preferred embodiment of the present invention, the α-haloketone of formula 4 is not isolated. Moreover, in a preferred embodiment of the present invention, the nitrogen atom of the amine substituent -NR^1R^2 of the ketone 3a is not protected.

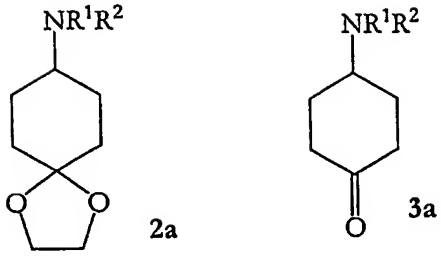
In a preferred embodiment of the first aspect of the invention, cyclohexandione is protected as a cyclohexandione monoethyleneketal 1, as shown in Figures 2 and 3.

A further preferred embodiment of the first aspect of the invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole 5, as outlined in Figure 3.

The process outlined in Figure 3 can readily be adapted to afford pramipexole I or its salts, for example by resolution of compound 5. Methods for resolving enantiomers are well known in the art and include, for example, chiral chromatography, fractional recrystallisation, derivatisation to form diastereomers and subsequent resolution, and resolution using enzymes.

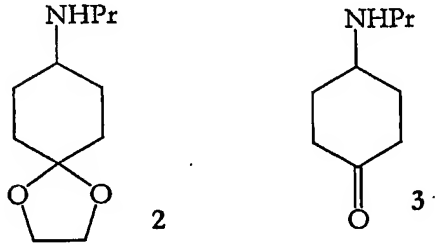
A further aspect of the invention is therefore pramipexole I and its salts, when prepared by a process according to the current invention.

Further aspects of the invention include novel compounds of the formula 2a or 3a, wherein R^1 and R^2 are as defined above, which are useful intermediates in the synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a.



2a 3a

Preferred embodiments of these aspects are compounds 2 and 3, as shown in Figure 3.



2 3

The process outlined in Figure 3 is an example of a procedure comprising the process of the current invention and detailed procedures for this process are found in the experimental section. Compounds of the current invention are also exemplified in Figure 3 and in the experimental section.

The process of the present invention is short, utilises readily available starting materials and does not involve the use of hazardous or difficult to handle reagents such as bromine, hydrazine or potassium chromate. Each step of the process of the present invention is high yielding and affords products of very high purity. Thus the process is easy to scale up for industrial scale manufacturing. Optionally 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles 5a and salts thereof may be manufactured in batches of 5kg or more, or even 10kg or more.

Experimental procedure

4-*n*-Propylamino-cyclohexanone-ethyleneketal 2

A mixture of *n*-propyl amine (162ml, 1.474mol) in methanol (500ml) was chilled to 0-5°C. To this solution was added methanolic hydrochloric acid (155ml, 44.47%) dropwise over a period of 30 minutes to achieve a pH of 6-7. Cyclohexandione monoethyleneketal **1** (100g, 0.641mol) was charged at 5°C and the reaction was stirred for 15 minutes. Sodium cyanoborohydride (60g, 0.952mol) was added in 15 minutes at 5°C. The pH increased to about 8 and methanolic hydrochloric acid (15ml, 44.47%) was added to bring the pH to 6-7. The reaction was allowed to come to 24-26°C. Stirring was continued for 2 hours. Methanol was distilled off (450ml). Sodium carbonate (95g, 0.896mol) was dissolved in water (850ml) and charged to the reaction mass at ambient temperature in one shot. The reaction mass was extracted with dichloromethane (2500ml). The dichloromethane layers were combined and dried over sodium sulfate (8.5g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product **2** was light yellow viscous oil. The weight of the product **2** obtained was 135g (105.8%); GC purity 97.74%.

^{1}H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr); 1.5-1.7 (m, 7H, $C\underline{H}_2CH_3$ of *n*Pr and 5H of cyclohexyl ring); 1.75-1.85 (m, 2H, 2H of cyclohexyl ring); 1.95-2.05 (m, 1H, 1H of cyclohexyl ring); 2.75 (t, 2H, $C\underline{H}_2CH_2CH_3$ of *n*Pr); 3.75-3.85 (m, 1H, NHCH); 3.9 (s, 2H, CH_2 of ethylene ketal) and 4.0 (s, 2H, CH_2 of ethylene ketal).
^{13}C NMR (δ ppm): 11.7 (CH_3 of *n*Pr); 21.8 ($\underline{C}H_2CH_3$ of *n*Pr); 28.5 (C-3 and C-5); 33.1 (C-2 and C-6); 48.3 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 55.8 (C-4); 64.5 (C of ethylene ketal); 64.6 (C of ethylene ketal); 108.1 (C-1).

4-*n*-Propylamino-cyclohexanone **3**

4-*N*-propylamino-cyclohexanone-ethyleneketal **2** (134g, 0.673mol) was taken in tetrahydrofuran (268ml) and cooled to 4-6°C. Concentrated hydrochloric acid (178ml, 2.01mol) was diluted with water (2144ml) and the mixture was cooled to 4°C. This diluted hydrochloric acid was added to the reaction mixture at 4-6°C in 15 minutes. The reaction was allowed to come to 24-26°C and stirring was continued for 24 hours. The reaction mass (2750ml) was concentrated to 1800ml at 50°C and 35mbar pressure. Sodium carbonate (148g, 1.4mol) was added to achieve

pH 10. The reaction mixture was extracted with dichloromethane (3670ml). The dichloromethane layers were combined and dried over sodium sulfate (20g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product 3 was yellow viscous oil. The weight of the product 3 obtained was 52.5g (52.84%); GC purity 86.07%.

^{1}H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr); (m, 2H, $C\underline{H}_2CH_3$ of *n*Pr); 1.6-1.75 (m, 2H, 2H of cyclohexyl ring); 2.05-2.15 (m, 2H, 2H of cyclohexyl ring); 2.2-2.3 (m, 2H, 2H of cyclohexyl ring); 2.4-2.55 (m, 2H, 2H of cyclohexyl ring); 2.55-2.65 (t, 2H, $C\underline{H}_2CH_2CH_3$ of *n*Pr); 2.9-3.0 (m, 1H, NHCH).
^{13}C NMR (δ ppm): 12.3 (CH_3 of *n*Pr); 24.0 ($\underline{C}H_2CH_3$ of *n*Pr); 32.6 (C-3 and C-5); 39.1 (C-2 and C-6); 50.0 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 54.4 (C-4); 211.9 (C-1).

2-Amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole 5

4-*n*-Propylamino-cyclohexanone 3 (5g, 32.26mmol) was charged in absolute ethanol (50ml) at 24-26°C. Iodine (8.5g, 33.5mmol) was added to it under stirring followed by thiourea (5g, 65.7mmol) at 24-26°C. The reaction mass was refluxed for 32 hours. Heating was stopped and the reaction mass was allowed to cool to 24-26°C. It was maintained at that temperature for 20 hours. 2-Amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole dihydroiodide salt crystallized out of the solution. Ethanol (30ml) was distilled out on the rotavapor at 50°C and 100mbar. Acetone (50ml) was added and the solid was filtered. The solid was dried at 40°C and 15mbar. The weight of the product obtained was 8.5g (56%); HPLC purity 94.97%.

^{1}H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr) 1.6-1.8 (m, 2H, $C\underline{H}_2CH_3$ of *n*Pr); 2.0 (m, 1H, H-7a); 2.35 (m, 1H, H-7b); 2.7 (m, 3H, H-5a, H-8a, H-8b); 3.1 (m, 3H, H-5b and $C\underline{H}_2CH_2CH_3$ of *n*Pr); 3.7 (m, 1H, NHCH).
^{13}C NMR (δ ppm): 12.0 (CH_3 of *n*Pr); 21.0 ($\underline{C}H_2CH_3$ of *n*Pr); 22.2 (C-7); 25.5 and 26.8 (C-5 and C-8); 48.7 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 54.7 (C-6); 113.0 (C-4); 134 (C-9); 171.2 (C-2).
Mass Spec: M^+ 211 (expected 211).

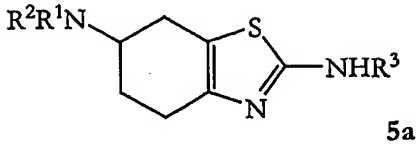
The 2-amino-6-*n*-propylamino-5,6,7,8-tetrahydrobenzthiazole dihydroiodide salt formed above (50g, 107.1mmol) was dissolved in water (200ml). The solution was cooled to 4°C and solid sodium hydroxide (50g, 1.25mol) was added in 15 minutes. The reaction was stirred for 1 hour at 24-26°C and the solid that precipitated out was filtered and dried at 40°C and 15mbar. The weight of the product 5 obtained was 17.07g (75.5%); HPLC purity 99.88%.

^{1}H NMR (δ ppm): 0.9-1.0 (t, 3H, CH_3 of *n*Pr); 1.5-1.6 (m, 2H, $C\underline{H}_2CH_3$ of *n*Pr); 2.1 (m, 1H, H-7a); 2.3 (m, 1H, H-7b); 2.5-2.6 (m, 5H, H-5a, H-5b, H-8a, H-8b and $C\underline{H}CH_2CH_3$ of *n*Pr); 2.9 (m, 2H, H-6 and $C\underline{H}CH_2CH_3$ of *n*Pr).
^{13}C NMR (δ ppm): 12.0 (CH_3 of *n*Pr); 24.6 ($\underline{C}H_2CH_3$ of *n*Pr); 26.6 (C-7); 30.7 and 30.9 (C-5 and C-8); 50.7 ($\underline{C}H_2CH_2CH_3$ of *n*Pr); 56.2 (C-6); 116.0 (C-4); 145 (C-9); 170.4 (C-2).
Mass Spec: M^+ 211 (expected 211).

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope of the invention, which is defined by the following claims.

Claims

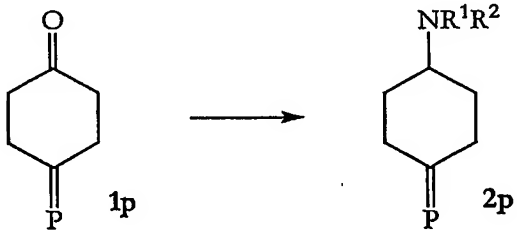
1. A process for the preparation of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a**



5a

or a salt thereof, comprising the steps of:

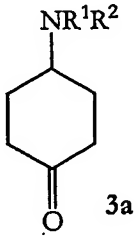
(a) reductively aminating a protected cyclohexandione **1p** with an amine R^1R^2NH to yield a protected 4-amino-cyclohexanone **2p**:



1p **2p** ,

wherein P is a protected ketone functionality, and R^1 and R^2 are any atom or group or, together with the nitrogen to which they are attached, form a ring;

(b) deprotecting the protected 4-amino-cyclohexanone **2p** to yield an unprotected 4-amino-cyclohexanone **3a**



3a ; and

(c) treating the unprotected 4-amino-cyclohexanone **3a** with iodine and a substituted thiourea $H_2N(C=S)NHR^3$, wherein R^3 is any atom or group, to yield the 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof.

2. A process as claimed in claim 1, wherein P is a cyclic ketal **1r**.

3. A process as claimed in claim 2, wherein P is a monoethyleneketal 1.

4. A process as claimed in any preceding claim, wherein R^1, R^2 and R^3 are independently hydrogen or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton.

5. A process as claimed in any preceding claim, wherein R^1, R^2 and R^3 are independently hydrogen or an unsubstituted alkyl, aryl or heteroaryl group, which does not include any heteroatoms N, O or S in its carbon skeleton.

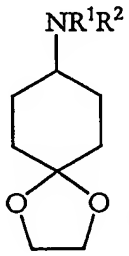
6. A process as claimed in any preceding claim, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton

7. A process as claimed in claim 6, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl.

8. A process as claimed in any preceding claim, wherein R^3 is hydrogen.

9. A process as claimed in any preceding claim, wherein the reductive amination of step (a) is carried out with $NaCNBH_3$.

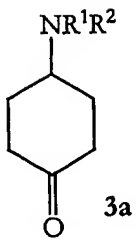
10. A 4-amino-cyclohexanone-ethyleneketal 2a



2a

for use in a process as claimed in any one of claims 1 to 9.

11. A 4-amino-cyclohexanone 3a



3a

for use in a process as claimed in any one of claims 1 to 9.

12. A compound as claimed in claim 10 or claim 11, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl.

13. A 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole 5a or a salt thereof, obtained by a process as claimed in any one of claims 1 to 9.

14. A compound as claimed in claim 13, wherein one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl, and wherein R^3 is hydrogen.

15. A compound as claimed in claim 13 or claim 14, wherein the compound is a di-hydrochloric acid salt.

16. A compound as claimed in any one of claims 13 to 15, comprising at least 95% of the (R)- or the (S)-enantiomer.

17. A compound as claimed in any one of claims 13 to 16 for use as a medicament.

18. A compound as claimed in claim 17, wherein the medicament is suitable for the treatment of a psychiatric or neurological disorder.

19. A compound as claimed in claim 18, wherein the psychiatric or neurological disorder is schizophrenia, Alzheimer's disease or Parkinson's disease.

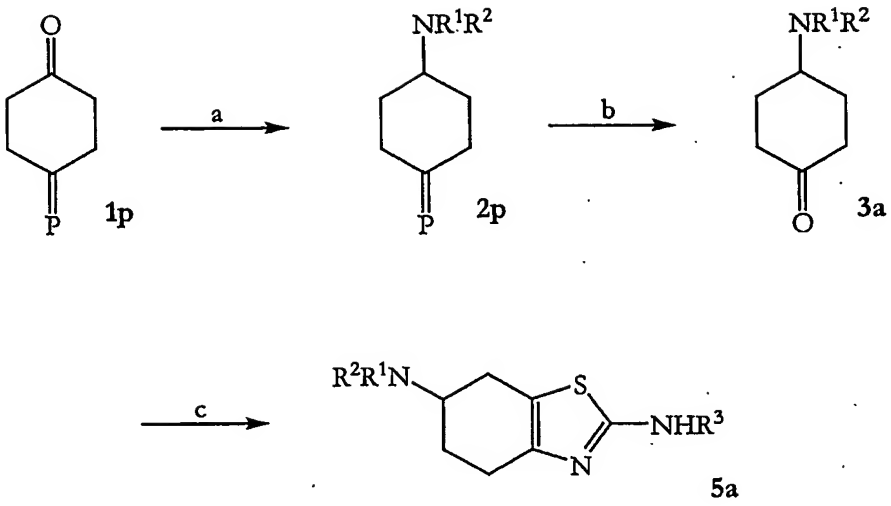
20. A pharmaceutical composition, comprising a compound as claimed in any one of claims 13 to 19 and a pharmaceutically acceptable carrier or diluent.

21. A pharmaceutical composition as claimed in claim 20, suitable for the treatment of a psychiatric or neurological disorder.

22. A pharmaceutical composition as claimed in claim 21, wherein the psychiatric or neurological disorder is schizophrenia, Alzheimer's disease or Parkinson's disease.

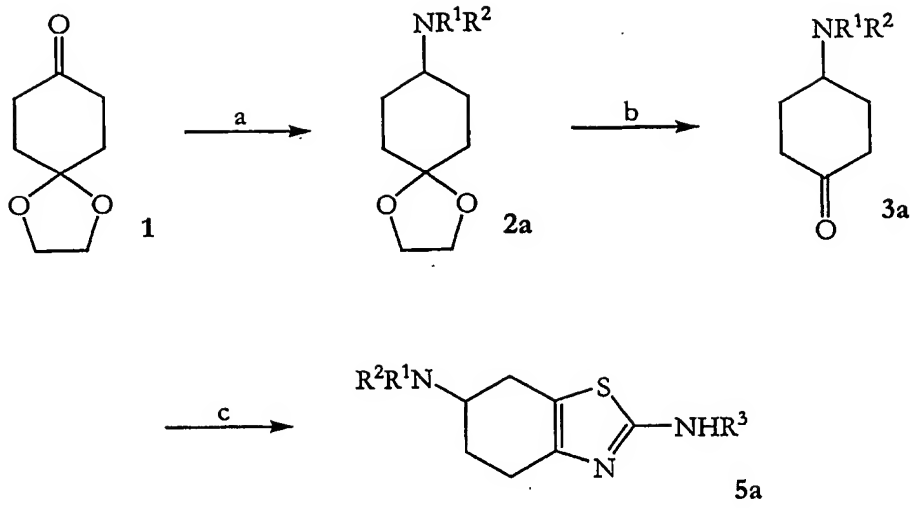
23. A method of treating a psychiatric or neurological disorder, comprising administering a therapeutically effective amount of a 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazole **5a** or a salt thereof as claimed in any one of claims 13 to 19 to a subject in need of such treatment.

24. A method as claimed in claim 23, wherein the psychiatric or neurological disorder is schizophrenia, Alzheimer's disease or Parkinson's disease.



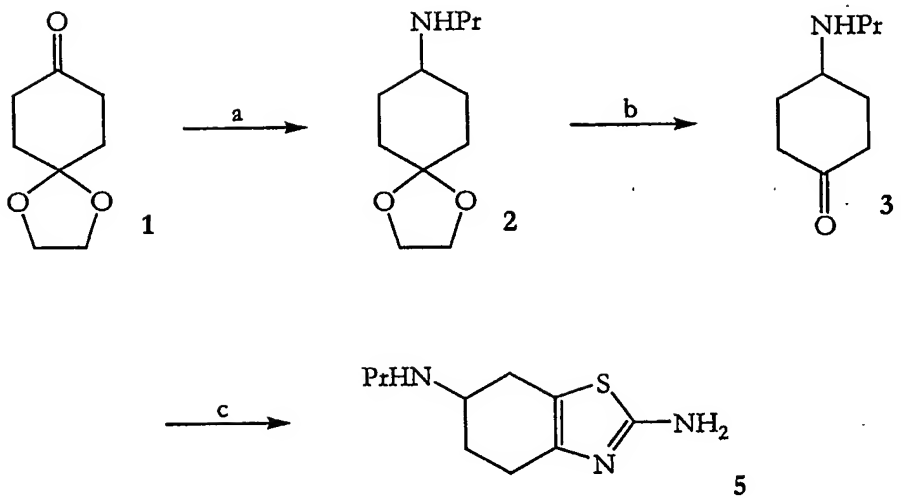
a: reductive amination with R^1R^2NH
b: deprotection
c: (i) iodine, $H_2N(C=S)NHR^3$; (ii) OH^-

Figure 1



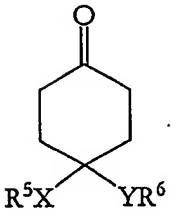
a: reductive amination with R^1R^2NH
b: deprotection
c: (i) iodine, $H_2N(C=S)NHR^3$; (ii) OH^-

Figure 2



a: *n*-propylamine, $NaCNBH_3$, MeOH/HCl
b: aq. HCl/THF
c: (i) iodine, $H_2N(C{=}S)NH_2$, ethanol, reflux; (ii) aq. NaOH

Figure 3



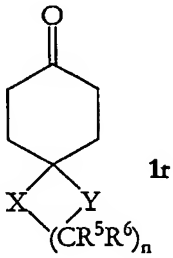
1q

X, Y = O, S or Se

R^5, R^6 = CO-R^7, $Si(R^7)_3$, or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton

R^7 = hydrogen or alkyl

and/or XR^5, YR^6 = CN



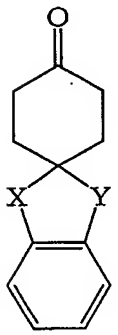
1r

X, Y = O, S, NR^7 or Se

n = 2 or 3

R^5, R^6 = hydrogen, halide, or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton

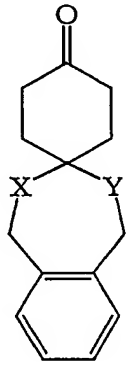
R^7 = hydrogen or alkyl



1s

X, Y = O, S or NR^6

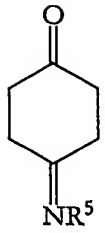
R^6 = hydrogen or alkyl



1t

X, Y = O, S or NR^6

R^6 = hydrogen or alkyl



1u

$R^5 = N(R^6)_2$ or OR^6

R^6 = hydrogen, or an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group, which may include one or more heteroatoms N, O or S in its carbon skeleton

Figure 4

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/GB 03/04022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/82 C07D317/72 C07C225/20 A61K31/429 A61P25/18
A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 207 696 A (LILLY CO ELI) 7 January 1987 (1987-01-07) page 7, line 16 -page 9, line 2; claims 1-6	10,11,13
A	page 7, line 16 -page 11, line 4 page 16, line 10 -page 18, line 15 claims 1-12	1-24

X	WO 02 22590 A (POSPISILIK KAREL; LEMMENS JACOBUS MARIA (NL); SYNTHON B V (NL); HO) 21 March 2002 (2002-03-21) claims 9-18,20-22	13-16
A	page 19, line 5 -page 2, line 17; claims 9-18,20-22	1-24

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 February 2004	18/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/GB 03/04022

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	column 3, line 34 -column 4, line 26 & US 4 886 812 A 12 December 1989 (1989-12-12) cited in the application & US 4 843 086 A cited in the application	1
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X	WO 96 18395 A (BOEHRINGER INGELHEIM KG; ROHDE FRANK A (DE); UPJOHN CO (US); HALL) 20 June 1996 (1996-06-20) claims	13-24
X	WO 99 59563 A (GOMEZ MANCILLA BALTAZAR; UPJOHN CO (US)) 25 November 1999 (1999-11-25) page 5, line 6 - line 18	13-15, 17-24
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-16

   Process for the preparation of compound 5a, which is already known from the art, from intermediates 2a and 3a, these intermediates, and the known product 5a per se.

2. Claims: 17-24

   Pharmaceutical compositions and methods making use of the known compound 5a.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/04022

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23 and 24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [X] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/GB 03/04022

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